Conclusions: Overall there were no differences in the ACE genotype frequency between the different groups. However, women with FH and AMI had the same ACE gene pattern which clearly differed from normals. We have previously found that women with acute MI who die during one year follow-up have very high DD frequency (46%), ID (42%) and II (27%). This very large group of FH patients needs to be followed in order to study whether ACE gene polymorphism also here is related to mortality.

4:45

723-4 A Mutation in the Methylenetetrahydrofolate Reductase Gene Is Not Associated With Increased Risk for Coronary Artery Disease or Myocardial Infarction

J.L. Anderson, G.J. King, M.J. Thompson, M. Todd, T.L. Bair, J.B. Muhlestein, J.F. Carlquist. *University of Utah and LDS Hospital, Salt Lake City, UT, USA*

Elevated plasma homocysteine has been identified as a risk factor for coronary atherosclerosis. Homocysteinemia results from a deficiency of methylenetetrahydrofolate reductase (MTHFR) activity which is instrumental in the conversion by methylation of homocysteine to methionine. A mild MTHFR deficiency which is associated with a thermolabile form of the enzyme has recently been associated with increased risk for coronary artery disease (CAD). In other studies, thermolabile MTHFR has also been shown to be linked to a C^{677} to T transition in the MTHFR gene. We therefore examined whether the C^{677} to T transition was associated with risk for CAD or myocardial infarction (MI). Blood was drawn from patients undergoing coronary catheterization and DNA extracted by a phenol-chloroform method. Genotyping was done by PCR amplification of a 198 bp segment of the MTHFR gene that brackets nt677. The amplicon was digested with the restriction enzyme *Hinf*I which recognizes a site created by the C to T substitution. Products were visualized by electrophoresis in 2% agarose with ethidium bromide staining. Coronary angiograms were read blinded to genotype results. Among patients (n = 521) with severe CAD (>60% stenosis) the mutant allele frequency was 34.6% compared with 35.6% for individuals with <10% stenosis (n = 166) (p = NS); 13.3% of patients compared with 14.0% of controls were homozygous for the mutation (p = NS). Among patients with a diagnosis of MI (n = 187) the mutant allele frequency was 33.3% compared with 32.0% for controls (n = 572) (p = NS); homozygosity among patients and controls was 11.2% and 11.0%, respectively (p = NS). Thus, patients with angiographic CAD or clinical MI do not show an increased frequency of the C^{677} to T mutation in MTHFR. Our findings do not support this mutation as the basis for increased risk for CAD or MI associated with homocysteinemia.

5:00

723-5 Angiotensin-Converting Enzyme Genotypes and Risk for Myocardial Infarction in Women

J.L. Anderson, J.F. Carlquist, G.J. King, L. Morrison, M.J. Thompsen, E. Ludwig, J.B. Muhlestein, T.L. Bair, R.H. Ward. *University of Utah and LDS Hospital, Salt Lake City, UT, USA, University of Oxford, Oxford, UK*

The human angiotensin-converting enzyme (ACE) occurs in two polymorphic forms: an insertion (I) allele which carries an inserted 287 base pair *Alu* element and a deletion (D) allele characterized by the absence of this element. Homozygosity for the D allele has been variously associated with myocardial infarction (MI), coronary artery disease (CAD) and idiopathic dilated cardiomyopathy in predominantly male populations. We tested for an increased association between this ACE polymorphism and MI in a sample comprised exclusively of women. For this study, genomic DNA was extracted using a phenol/chloroform method and precipitated with isopropanol. The ACE alleles were identified by the amplified fragment length polymorphism (AFLP) method which uses primers to bracket the insertion region in intron 16 and the polymerase chain reaction (PCR) to produce either a 490 bp product (I allele) or a 190 bp product (D allele). Products were electrophoresed on a 1.5% agarose gel and visualized by ethidium bromide staining. There was a significant increase in the frequency of the DD genotype among women who had a previous MI (n = 141) compared with matched controls without MI (with or without CAD; n = 323) (39.0% vs 29.0%, p < 0.05; relative risk (RR) = 1.55). In contrast, the D allele was found in combination with the I allele somewhat more frequently among controls than patients (48.0% vs 39.0%, RR = 0.69, p < 0.03) suggesting a possible protective effect for the heterozygous (ID) versus homozygous (DD) genotype. The frequencies of the II genotype were similar for patients and controls (21.9% and 22.9%, respectively; RR = 0.95). Consistent with findings in male-dominated populations, our results associate the ACE DD genotype with increased risk for MI in women. In contrast to other reports, the ID phenotype did not confer risk and tended to be protective, a finding that will require confirmation.

5:15

723-6 Serum Levels of Transforming Growth Factor-Beta 1 (TGF-β1) is Depressed in Women With Coronary Artery Disease

E.D. Afflu, M.A. Amine, L.T. Clark, O.A. Batuman. *SUNY Health Science Center at Brooklyn, NY, USA*

The antiinflammatory cytokine TGF-β1 is produced by all cell types within the vascular wall, in a latent form that required bioactivation by proteolysis, or acidification in vitro. In this study the clinical relevance of TGF-β1 in CAD was studied by correlating its serum levels with the extent of coronary artery disease in 61 consecutive females (age 40–78) with angiographically defined CAD stratified as involving: 0 vessels (n = 21, mean age 61.5), or 1–2 vessels (n = 21, mean age 62.1), or 3 vessels (n = 19 patients, mean age 61.6). Venous blood was obtained fasting, immediately prior to cardiac cath, and active and total TGFβ-1 in serum and plasma were measured by ELISA. Active TGF-β1 levels were always <5pg/ml. Total (active+latent) TGF-β1 was determined after acid activation of samples and serum and plasma levels showed a significant correlation. Mean serum TGF-β1 levels in 0, 1–2, and 3 vessel CAD groups were 78.2 ± 31.1 (± SD), 64 ± 19.5, and 58.7 ± 26.9, respectively. Difference between serum TGF-β1 levels of patients with no CAD, and with CAD, was significantly different (t = 2.39, p < 0.020). Difference between TGF-β1 levels in patients with no CAD, and 3 vessel CAD was also significant (t = 2.17 p < 0.03). We found a negative correlation between: 1) serum TGF-β1 levels and presence of CAD (r = −0.31, p < 0.022) (Spearman's rank correlation). We did not observe a correlation between serum TGF-β1 levels and serum Lp(a), Apo B, Apo A1, triglycerides, HDLC, LDLC, total cholesterol, or existence of unstable angina. We conclude that depressed levels of serum TGF-β1 in CAD correlate with disease severity.

724 Gene Polymorphism in Hypertension: Cardiovascular Correlates

Monday, March 17, 1997, 4:00 p.m.–5:30 p.m.
Anaheim Convention Center, Room B2

4:00

724-1 Is Angiotensin-Converting Enzyme I/D Polymorphism Involved in Cardiovascular Complications in Essential Hypertension?

M.L. De Buyzere, B.B. Wuyts, J.R. Delanghe, D.A. Duprez, G. Leroux-Roels, D.L. Clement. *University Hospital Gent, Belgium*

DD-genotype of the insertion/deletion (I/D) polymorphism of the angiotensin-I converting enzyme (ACE) has been incriminated to be a potent risk factor in ischemic heart disease. On the other hand, recent literature was unable to link (I/D)–ACE polymorphism with essential hypertension, (HT). Therefore, we aimed to study frequency of (I/D)–ACE genotypes in target organ damage in essential HT. A group of 305 patients was enrolled (168 males, 137 females, age 55 ± 13 years). One hundred and five patients (34.3%), had a DD-genotype, 144 (47.3%) a DI-genotype and 56 patients (18.4%) a II-genotype. The D-allele frequency of 0.58 was comparable with D-allele frequency (0.61) in a control group of 115 healthy subjects from the same region. Table summarizes age, detection of hypertension, number of antihypertensive drug classes needed to reduce BP to <95 mmHg, left ventricular hypertrophy (LVH), infarction (AMI) and ACE activity for the three genotypes.

Table	DD (n = 105)	DI (n = 144)	II (n = 56)
Age (years)	55 ± 13	54 ± 13	57 ± 13
Age at detection (yr)	46 ± 12	44 ± 12	47 ± 13
Number of drug classes	1.9 ± 0.8	1.9 ± 0.9	1.9 ± 1.0
LVH (%)	38	43	20
AMI (%)	34	54	12
ACE activity (U/L) (* p < 0.01)	71 ± 24*	57 ± 27	40 ± 24

The higher ACE activity in DD-genotype is in agreement with earlier findings.

In conclusion, DD-genotype of the (I/D)-ACE polymorphism was not over-represented in cardiovascular complications in essential hypertension.